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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530 VIRGINIA ROAD P.O. BOX 9133 CONCORD, MA 01742-9133				
			EXAMINER HALVORSON, MARK	
			ART UNIT 1642	PAPER NUMBER

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/678,790	Applicant(s) CROCE ET AL.	
	Examiner Mark Halvorson	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 November 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-93 is/are pending in the application.
- 4a) Of the above claim(s) 1-5, 8-16, 18 and 20-93 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 6, 7, 17 and 19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) ☐ Notice of Informal Patent Application |
| 3) ☒ Information Disclosure Statement(s) (PTO/SB/06)
Paper No(s)/Mail Date <u>12/3/2003</u> . | 6) ☒ Other: <u>sequence search</u> . |

DETAILED ACTION

Claims 1-93 are pending.

Election/Restrictions

Applicant's election of Group II, claims 6, 7, 17 and 19, in the reply filed on Nov 9, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-5, 8-16, 18 and 20-93 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 6, 7, 17 and 19 are currently under prosecution.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 14 line 25. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6, 7, 17 and 19 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial utility, a credible asserted utility, or a well-established utility.

Claims 6, 7, 17 and 19 are drawn to a Tcl-1b protein having the amino acid sequence, of SEQ ID NO:39.

The specification describes a Tcl1b gene that is located at 14q32.1, approximately 16 kb from the oncogene TCL1 (page 3, line 4 to page 4 line 12). The Tcl1b gene encodes a protein that has 22% sequence identity with Tcl1 (see sequence results). Tcl1b RNA is expressed in a variety of tissues, including one of four T cell leukemia cell lines and two of six EBV transformed lymphoblastoid B cell lines that have elevated Tcl1 RNA expression (page 15 line 20 to page 16 line 12). The specification does not disclose that expression of Tcl1b RNA is elevated in primary tumors.

The art generally acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Scott et al (Nature Genetics, 1999, 21:440-443) teach that the function of newly identified gene products is unpredictable even when the database searches reveal significant homology to proteins of known function. Scott et al teaches that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence

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similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. states that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Skolnick et al. (2000, Trends in Biotech. 18:34-39) also states that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural

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similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Furthermore, Applicant has not demonstrated expression levels of Tcl1b protein or any link between RNA expression of Tcl1b and protein expression of Tcl1b. It is well known and recognized in the art that mRNA detection is not an indication of protein production level. In particular, Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, col 2) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, col 2) that there are presumably at least three reasons for the poor correlations

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generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page col 2) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood.

The specification does not provide a relationship between the expression of Tc1b protein to any specific diseases for the purposes of diagnosis and/or treatment. The specification does not provide any guidance in terms of what expression patterns are needed for diagnosing and what end points are required for the treatment of cancer.

Since the specification has failed to establish a real world use of the claimed protein, a substantial utility has not been clearly set forth. Hence, further research would be required to identify and reasonable confirm the "real world" use for Tc1b. As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility Guidelines Training Materials).

Claims 6, 7, 17 and 19 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a substantial asserted utility

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or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

After further research, a specific and substantial credible utility might be found for the claimed invention. This further characterization, however, is part of the act of invention and until it has been undertaken, applicant's claimed invention is not complete. Therefore it is concluded that the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention without undue experimentation.

Claim 17 is further not enabled for a fusion protein comprising a Tc1-1b protein sequence of at least 10 amino acids linked to a non-Tc1-1b. As written the claim is interpreted to encompass a fusion protein comprising a multitude of amino acid sequence which are not necessarily contiguous.

The specification discloses only the full length Tc1 1b protein comprising the amino acid sequence of SEQ ID NO:39.

Claim 17 encompasses a multitude of amino acid sequences. It would require undue experimentation to use the multitude of claimed amino acid sequences, especially considering the lack of known function of the full length amino acid sequence of Tc1-1b.

Claim 6 is also rejected under 35 USC 101 because the claimed invention is directed towards non-statutory subject matter. Claims 6, as written, does not sufficiently distinguish over proteins as they exist naturally because the claims do not particularly point out any non-naturally occurring difference between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring

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products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as taught by the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 19 is drawn to a genus of peptides comprising an amino acid sequence having at least 70% amino acid sequence identity to an amino acid sequence depicted in SEQ ID NO:39, over a contiguous sequence of at least 25 amino acids.

The specification discloses a single Tc1b peptide comprising the amino acid sequence of SEQ ID NO:39.

The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written

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description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials.” *Id.* At 1567, 43 USPQ2d at 1405. The court concluded that “naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.” *Id.*

The Federal Circuit has recently clarified that a molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by “show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.” *Id.* At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Thus, the instant specification may provide an adequate written description of Tc11b peptides, per Lilly by structurally describing a representative number of peptides that function as claimed or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the genus of Tc1b peptides in a manner that satisfies either the Lilly or Enzo standards. There are insufficient structural features common to all members of the genus of Tc1b peptides. The genus of Tc1b peptides comprises any peptide that has 70% sequence identity to 25 contiguous amino acids of SEQ ID NO:39. This encompasses a multitude of peptides. There is virtually no structural similarity between the genus of Tc1b peptides as defined in the specification. The only Tc1b peptide specifically described in the specification is the peptide comprising the amino acid sequence of SEQ ID NO:39. One species does not sufficiently describe the genus of Tc1b peptides and does not meet the standard set forth in Lilly.

The instant specification may also provide an adequate written description of the genus of polypeptide antagonists if the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. The specification discloses only one Tc1b peptide comprising the amino acid sequence of SEQ ID NO:39. Furthermore, the specification does not disclose any amino acid sequence that correlates with a known function of the Tc1b peptide. The specification does not disclose any known function of the one identified species of Tc1b peptides, the Tc1b peptide comprising the amino acid sequence of SEQ ID NO:39. Thus, the specification does not describe sufficient structural characteristics that correlate with the ability of the genus of Tc1b peptides to function as contemplated by the specification and for the reasons set forth above do not meet the standards set forth by Enzo.

Thus, the specification does not provide an adequate written description of the genus of genus of polypeptide antagonists of claim 19 that is required to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 7 is rejected under 35 U.S.C. 102(e) as being anticipated by Russo et al (U.S. Patent No: 5985598, issued November 16, 1999, filed October 27, 1994).

Claim 7 is drawn to an isolated amino acid sequence of SEQ ID NO:39. The peptide fragments encompassed by “an amino acid of SEQ ID NO:39” include small amino acid fragments of SEQ ID NO:39.

Russo discloses SEQ ID NO:2 (human Tcl-1) that includes fragments of 5 amino acids that are identical to amino acid fragments of SEQ ID NO:39.

Summary

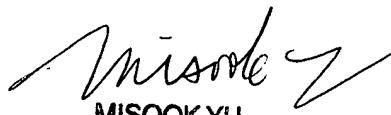
No claims allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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